3,3'-Dipyrrrolyl sulfides, useful building blocks for the syntheses of macrocycles containing dipyrromethene units

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Abstract: 5,5'-Dicarboxy-3,3'-dipyrrolyl sulfide was condensed with 5,5'-diformyl-3,3'-dipyrrolyl sulfide or 5,5'-diformyl dipyrromethene under acidic conditions to produce, in high yields, macrocycles containing four dipyrromethene units.

Key words: 3,3-dipyrrolyl sulfide, cyclopolyppyrrole, dipyrromethene, macrocycle.

Introduction

In recent years expanded porphyrins and macrocycles related to porphyrins have been receiving increasing attention (1-4), and they are being utilized in fields such as photodynamic therapy (PDT), neutral substrate binding, and anion recognition.

Macrocycles containing six (3), eight (4, 5), ten (6), and twelve (7) pyrrolic rings have been reported, and recently meso-aryl-substituted expanded porphyrins containing up to 12 pyrrolic rings have been described (8). We report here a new type of macrocycle, which contains dipyrromethene units linked by sulfur atoms prepared via a McDonald synthesis.

Results and discussion

5,5'-Difomyl-2,2'-dipyrrolyl sulfides have been known for many years as intermediates in the synthesis of thiaporphyrins (Scheme 1) (9, 10). We attempted to condense a 5,5'-difomyl-3,3'-dipyrrolyl sulfide 6 with a 5,5'-dicarboxy-3,3'-dipyrrolyl sulfide 3 under acidic conditions and were surprised to find that the product was not the expected compound 7, but the macrocyclic product 8, which contained eight pyrrole rings (Schemes 2 and 3) where the dipyrromethene units were linked by sulfur atoms.

The precursor 5,5'-dicarboxy-3,3'-dipyrrolyl sulfide 3 was prepared from 2-ethoxycarbonyl-3,5-dimethylpyrrole via two steps: reacting 1 with sulfur dichloride (11), followed by treatment with sodium hydroxide to give the diacid 3. Another important intermediate 6 was synthesized from 1 in 3 steps. Thus compound 1 was saponified and decarboxylated under basic condition (sodium hydroxide) at 180 °C using ethylene glycol as solvent to yield 2,4-dimethylpyrrole (4), which was converted to 2-formyl-3,5-dimethylpyrrole (5) under Vilsmeier formylation conditions. Coupling 5 with sulfur dichloride gave the key intermediate compound 6 in high yield (11).

Compound 8 is formally a dimer of 7 (Scheme 3), which was formed in a [2 + 2 + 2 + 2] condensation from 2 equiv each of 3 and 6.

To extend our work, we tried to condense 3 with 9 and 6 with 10 under similar acidic conditions. Once again, these reactions did not provide the [2 + 2] product 11, but the [2 + 2 + 2 + 2] condensation product 12 (Scheme 4). Similar [2 + 2 + 2 + 2] condensations have previously been observed by Sessler, Vogel, and their co-workers (2, 4, 5, 12). In general these reactions occurred with yields usually below 20%, lower than those reported here, which range from 80 to 90%.

The composition of the new macrocycle 8 was established by combustion analysis, UV-vis, and FAB mass spectrometry. As expected, 8 does not possess macrocyclic aromaticity.


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Scheme 2. Reagents and condition: (a) SCl₂-CH₂Cl₂, 50 °C; (b) NaOH-EtOH, reflux 3 h, then HOAc, pH = 4; (c) NaOH glycol, 180 °C; (d) POCl₃-DMF, then NaOH; (e) SCl₂-CH₂Cl₂, -60 °C.

Since the conjugated system is interrupted by the sulfur bridges. The molecule has high symmetry, which is consistent with its ¹H and ¹³C NMR spectra; there are two types of CH₃ signals, one for α-CH₃ and the other for β-CH₃ groups, and one -CH= signal at 7.00 ppm. Moreover, the ¹³C NMR of 8 in TFA-d showed 5 sp² signals, which correspond to one -CH= and four carbons in each pyrrole ring. Compound 8 has very low solubility in most common solvents such as dichloromethane, chloroform, methanol, acetone, DMF, DMSO, acetic acid, acetonitrile, THF, dioxane, and pyridine. However, it is soluble in trifluoroacetic acid, in which it displays a beautiful purple color. In other solvents 8 can have a red to yellow color depending on its degree of protonation. Macrocycle 12 was characterized as above, and its optical properties are similar to those of macrocycle 8; 12 is more soluble than 8 in most solvents.
Experimental section

General

All reagents and solvents were purchased and used as received. Melting points were determined on a Thomas hot stage or Buchi apparatus and are uncorrected. $^1$H and $^{13}$C NMR spectra were recorded on a Bruker AC-200 or AMX-300 instrument. The high- and low-resolution mass spectra were obtained by the departmental mass spectrometry service laboratory. Combustion analyses were performed by the departmental microanalytical laboratory. Optical spectra were recorded on an HP8452A Photo diode array spectrophotometer (instrumental precision ±2 nm).

Bis(5-ethoxycarbonyl-2,4-dimethylpyrrole-3-yl)sulfide (2) and bis(5-formyl-2,4-dimethyl pyrrole-3-yl)sulfide (6) were prepared according to literature procedures (11).

Bis(5-carboxy-2,4-dimethylpyrrole-3-yl) sulfide (3)

Bis(5-ethoxycarbonyl-2,4-dimethylpyrrole-3-yl) sulfide (20 g, 55 mmol) was suspended in ethanol (180 mL). The mixture was stirred, and a solution of sodium hydroxide (8.8 g in 20 mL water) was added all at once. The suspension was then stirred under reflux for 3 h, and the solvent was then removed under vacuum. The residue was stirred with brine (100 mL) at -10°C; then acetic acid was added dropwise until pH 4. The precipitate was collected by suction filtration and washed with cold water. After drying under vacuum, the desired product was obtained as a pink solid (16.2 g, 96%).

mp 220 °C (decomposition (dec)). $^1$H NMR (200 MHz, DMSO-d$_6$) (ppm) δ: 2.20 (s, 12H, 4CH$_3$), 11.20 (s, 2H, 2NH), 12.00 (s, 2H, COOH). $^{13}$C NMR (75 MHz, DMSO-d$_6$) (ppm) δ: 11.26, 11.72, 111.57, 119.53, 127.35, 133.68, 163.77 (COOH). C$_{14}$H$_{16}$N$_2$O$_4$S required: C 54.54, H 5.19, N 8.96; found: C 54.06, H 5.54, N 8.86.

Synthesis of 8-2TFA

5,5'-Dicarboxy-3,3'-dipyrryl sulfide (3) (200 mg, 0.66 mmol) was suspended in trifluoroacetic acid (10 mL) and stirred at 40 °C until all the solid had dissolved. The red mixture was cooled to room temperature. To this solution was added the 5,5'-diformyl-3,3'-dipyrrolyl sulfide (6) (181 mg, 0.66 mmol) under continuous stirring. After 10 min, a mixture of dichloromethane (20 mL), methanol (20 mL), and hydrogen bromide (3 mL, 48% in acetic acid) was added. The red mixture was allowed to stir overnight at room temperature. Anhydrous ether (100 mL) was added. The suspension was allowed to stir for another 2 h. The red solid was collected by suction filtration and washed with anhydrous ether to give 8 (378 mg, 92%).

mp 295 °C (dec). $^1$H NMR (CDCl$_3$, 200 MHz) (ppm) δ: 0.85 (t, J = 7.32 Hz, 12H, 4CH$_2$CH$_3$), 2.15 (s, 12H, 4CH$_3$), 2.21 (s, 12H, 4CH$_3$), 2.31 (s, 12H, 4CH$_3$), 2.50 (q, J = 7.32 Hz, 8H, 4CH$_2$), 7.12 (s, 4H, 4-CH$_3$), 14.10 (s, 4H, 4NH), 14.35 (s, 4H, 4NH). $^{13}$C NMR (TFA-d, 75 MHz) (ppm) δ: 10.05, 11.01, 13.91, 14.11, 17.50, 23.59, 118.25, 121.97, 126.97, 132.32, 146.31, 149.11, 150.09, 157.40. UV-vis (CH$_2$Cl$_2$ + TFA) $\lambda_{\text{max}}$ (nm) (ε): 450 (109 600), 520 (96 000). FAB-MS m/e: 941 ([M + 1$^+$$]$. HR-MS (LSIMS, thioglycerol), calcd. for [C$_{32}$H$_{56}$N$_8$S$_4$ + 1$^+$]: 941.50744; found: 941.50744. Conclusion

Vogel (12) has noted that the equimolar MacDonald-type condensation of a diformyl bipyrrole with a dipyrrole dicarboxylic acid gives, in most cases, octahyrins as the sole products. The present study extends these observations and...
Chen and Dolphin shows that related octapyrroles can be produced, in high yield, from 3,3'-dipyrryl sulfides via a \([2 + 2 + 2 + 2]\) MacDonald synthesis. Further work on the application of the present method for the synthesis of cyclooctapyrroles and cyclopoly pyrroles using 3,3'-dipyrrromethanes is in progress.

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**References**